Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 3, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.040

Increased Need for Right Ventricular Support in Patients With Chemotherapy-Induced Cardiomyopathy Undergoing Mechanical Circulatory Support

Outcomes From the INTERMACS Registry (Interagency Registry for Mechanically Assisted Circulatory Support)

Guilherme H. Oliveira, MD,* Matthias Dupont, MD,† David Naftel, PHD,‡ Susan L. Myers, BBA,‡ Ya Yuan, BS,‡ W. H. Wilson Tang, MD,* Gonzalo Gonzalez-Stawinski, MD,§ James B. Young, MD,* David O. Taylor, MD,* Randall C. Starling, MD, MPH*

Cleveland, Ohio; Genk, Belgium; Birmingham, Alabama; and Dallas, Texas

Objectives The aim of this study was to investigate the use of durable mechanical circulatory support (MCS) in patients with chemotherapy-induced cardiomyopathy (CCMP) and determine their outcomes and survival in comparison to that of other patients with end-stage heart failure treated similarly.

Background Patients with end-stage heart failure as a result of CCMP from anthracyclines are often precluded from heart transplantation because of a history of cancer. In such patients, durable MCS may offer an important chance for life prolongation. Yet, there are no data to support the use of MCS in this increasingly prevalent group of patients.

Methods We searched 3,812 MCS patients from June 2006 through March 2011 in the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) database for the diagnosis of CCMP. We compared characteristics, outcomes, and survival between CCMP patients and patients with nonischemic cardiomyopathy and ischemic cardiomyopathy.

Results Compared with patients with nonischemic cardiomyopathy and ischemic cardiomyopathy, patients with CCMP were overwhelmingly female (72% vs. 24% vs. 13%, $p = 0.001$), had MCS more often implanted as destination therapy (33% vs. 14% vs. 22%, $p = 0.03$), required more right ventricular assist device support (19% vs. 11% vs. 6%, $p = 0.006$), and had a higher risk of bleeding ($p = 0001$). Survival of CCMP patients was similar to that of other groups.

Conclusions CCMP patients treated with MCS have survival similar to other MCS patients despite more frequent need for right ventricular assist device support and increased bleeding risk. (J Am Coll Cardiol 2014;63:240–8) © 2014 by the American College of Cardiology Foundation

Heart failure from chemotherapy-induced cardiomyopathy (CCMP) is a major cause of morbidity and mortality in breast and childhood cancer survivors. Despite recent advances in cancer therapy with the advent of newer, potentially cardiotoxic drugs, anthracyclines remain the major class of agents proven to lead to end-stage heart failure, and we therefore use CCMP as synonymous with anthracycline-induced cardiomyopathy (1–3). CCMP is known to have a worse prognosis compared with other heart failure causes (4) and potentially leads to end-stage heart failure that requires advanced therapies (5). However, unlike other types of cardiomyopathies, patients with CCMP are often not candidates for transplantation because of previous or concurrent cancer (6). Additionally, there have been concerns that survival could be limited by accelerated recurrence of malignancies because of immunosuppression.

See page 249

From the *Advanced Heart Failure and Transplantation Center, Division of Cardiovascular Medicine, Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio; †Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; ‡Cardiovascular Surgery Research, University of Alabama at Birmingham, Birmingham, Alabama; and the §Department of Cardiothoracic Surgery, Baylor Medical Center, Dallas, Texas. Ms. Myers is a consultant for HeartWare and Thoratec. Dr. Oliveira is now affiliated with the Advanced Heart Failure and Transplantation Center, Division of Cardiovascular Medicine, Harrington Heart and Vascular Institute University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 11, 2013; revised manuscript received August 30, 2013, accepted September 11, 2013.

In such patients, alternate modes of advanced therapies, such as durable mechanical circulatory support (MCS), may offer hope for life prolongation (7,8) and have thus been used sporadically in highly-selected patients with varying success (9,10). Yet, outcomes are unknown, and the safety and appropriateness of MCS for patients with CCMP have not been studied.

We, therefore, investigated the use of MCS in CCMP patients, described their baseline characteristics and device implantation strategies, and compared their outcomes with those of patients with ischemic cardiomyopathy (ICMP) and nonischemic cardiomyopathy (NICMP).

Methods

Interagency Registry for Mechanically Assisted Circulatory Support. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database is a National Heart, Lung, and Blood Institute–funded national registry of patients treated with U.S. Food and Drug Administration–approved mechanical circulatory support devices for the treatment of advanced heart failure (11). Participation is mandatory for Centers for Medicare and Medicaid Services–approved MCS implantation centers, all information is audited, and a Medical Events Committee reviews adverse events for medical reasonableness and internal consistency. The University of Alabama was entrusted with the Data Coordinating Center and has created and maintained the registry since 2005.

Patient population. Using the INTERMACS registry, we retrospectively identified prospectively entered patients with CCMP who received MCS during the period of June 2006 through March 2011. To ensure that no patient was missed, we included anthracyclines, doxorubicin, Adriamycin, and chemotherapy as searchable terms in the database.

Patient characteristics and outcomes. We compared CCMP patient pre-implant characteristics; implantation strategies; and clinical, echocardiographic, and hemodynamic profiles with those of patients with ICMP and NICMP.

The primary outcome was all-cause mortality, with data censored at transplantation or device explantation after myocardial recovery. Secondary outcomes were time to first major bleed, device malfunction, right ventricular (RV) failure, infection, neurological dysfunction, and need for RV assist device (RVAD) support at the time of or subsequent to left ventricular assist device (LVAD) implantation.

Statistical analyses. Survival rates were calculated using the Kaplan-Meier method. Categorical characteristics and outcomes were compared using chi-square and Fisher exact tests. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Time-related events (death, bleeding, device malfunction, infection, right heart failure, and neurological dysfunction) were estimated using the Kaplan-Meier method. Comparisons of freedom from event curves were made using the log-rank test, which is the univariate equivalent of Cox proportional analysis. Categorical pre-implantation data were compared across groups using the chi-square test for equality of proportions or, when the sample size was small, the Fisher exact test. Continuous pre-implantation data were compared across groups using a *t* test in the original scale or, when appropriate, a *t* test after arithmetic transformations for skewed distributions. All analyses were performed using SAS version 9.13 Unix statistical software (SAS Institute Inc., Cary, North Carolina).

Abbreviations and Acronyms

CCMP = chemotherapy-induced cardiomyopathy
ICMP = ischemic cardiomyopathy
LVAD = left ventricular assist device
MCS = mechanical circulatory support
NICMP = nonischemic cardiomyopathy
RV = right ventricular
RVAD = right ventricular assist device

Results

We identified 75 patients (2%) from 3,812 patients implanted between June 2006 and March 2011. Their comparative pre-implantation characteristics are displayed in Table 1. Female patients predominated in the CCMP group (72%), whereas in the NICMP and ICMP groups, the majority of patients were male (76% and 87%, respectively). Patients with CCMP had generally fewer comorbidities than both ICMP and NICMP patients, with lower rates of diabetes, alcohol abuse, and tobacco use. Of the 75 patients with CCMP, 39 (52%) had a history of breast cancer, 25 (33%) had lymphoma and other hematological cancers, 2 (3%) had renal cancer, and 9 (12%) had unspecified malignancies.

There were no differences in the prevalence of New York Heart Association functional class IV, patient profiles, inotrope use, or left ventricular ejection fraction severity. Also, indexed left ventricular end-diastolic diameter was not different between the groups.

The rate of use of automatic implantable defibrillators was 66% in the CCMP group and 77% in both the ICMP and NICMP groups ($p = 0.03$).

In this series, 84% of CCMP patients were treated with continuous flow devices, which was not statistically different from the ICMP (75%, $p = 0.06$) and NICMP (78%, $p = 0.25$) patients.

Implantation strategy. CCMP patients were more likely to have MCS implanted as destination therapy (33%) compared with patients with both ICMP (14%, $p < 0.0001$) and NICMP (23%, $p < 0.03$). If the implantation strategy was a bridge to transplantation, there were no differences in the rates of listing.

RV dysfunction. Surrogate markers of RV dysfunction were significantly more common in patients with CCMP compared with ICMP and NICMP patients. Pulmonary systolic pressures in the CCMP group were significantly lower than in both ICMP and NICMP patients (43.96 vs. 51.16 vs. 49.35 mm Hg, respectively; $p = 0.0015$). Also, right atrial pressure was higher (16.48 vs. 12.49 vs. 13.45 mm Hg, respectively; $p = 0.01$) and severe tricuspid

Table 1 Baseline Characteristics of CCMP Compared With NICMP and ICMP Patients

	CCMP (n = 75)	NICMP (n = 2,392)	p Value	ICMP (n = 1,345)	p Value
Demographic					
White, %	64.0	64.0	0.92	80.0	0.0006
Male, %	28.0	76.0	<0.0001	87.0	<0.0001
Age, yrs	53.0	51.0	0.41	60.0	<0.0001
Married, %	63.0	62.0	0.76	72.0	0.12
Body mass index, kg/m^2	26.0	28.9	<0.0001	28.0	0.0019
Body surface area, m^2	1.84	2.09	<0.0001	2.08	<0.0001
Clinical, %					
Diabetes	25.0	31.0	0.29	46.0	0.0004
Inotropes	89.0	83.0	0.18	80.0	0.06
Ascites	13.0	9.0	0.29	9.0	0.24
INTERMACS patient profile level					
1	20.0	22.0	0.67	20.0	0.99
2	47.0	43.0	0.55	42.0	0.39
3	20.0	19.0	0.39	19.0	0.33
4	7.0	10.0	0.34	13.0	0.33
5	1.0	2.0	0.61	3.0	0.61
6	1.0	1.0	0.95	2.0	0.84
7	0.0	1.0	0.36	1.0	0.33
Bridge to transplantation					
Listed	35.0	42.0	0.21	34.0	0.98
Likely to be listed	19.0	27.0	0.10	27.0	0.12
Moderately likely to be listed	9.0	10.0	0.80	10.0	0.84
Unlikely to be listed	1.0	3.0	0.43	4.0	0.23
Destination therapy	33.0	14.0	<0.0001	23.0	0.03
NYHA functional class IV	84.0	81.0	0.55	83.0	0.85
Diagnosis coronary artery disease	0.0	16.0	0.0002	100.0	<0.0001
Cerebrovascular accident	7.0	7.0	0.93	8.0	0.69
Transient ischemic attack	7.0	3.0	0.12	4.0	0.27
Cancer	89.0	4.0	<0.0001	7.0	<0.0001
Current smoker	1.0	12.0	0.01	15.0	0.0016
Current drug abuse	1.0	3.0	0.45	2.0	0.87
Alcohol abuse history	5.0	16.0	0.01	18.0	0.01
Blood type O	62.0	74.0	0.07	45.0	0.0049
Rheumatological disease	3.0	5.0	0.42	4.0	0.67
Hepatitis B	0	1.0	0.31	2.0	0.26
Hepatitis C	4.0	2.0	0.17	2.0	0.30
Dialysis	1.0	3.0	0.37	2.0	0.56
History of coronary artery bypass graft	1.0	8.0	0.03	43.0	<0.0001
Implantable cardioverter-defibrillator	66.0	77.0	0.03	77.0	0.03
Intra-aortic balloon pump	32.0	35.0	0.59	36.0	0.48
Ventilator	9.0	12.0	0.48	12.0	0.48
Peripheral vascular disease	3.0	4.0	0.54	10.0	0.04
Carotid artery disease	4.0	5.0	0.81	17.0	0.01
Beta-blockers	82.0	74.0	0.12	75.0	0.18
ACE inhibitors	68.0	53.0	0.02	51.0	0.01

Continued on the next page

regurgitation was more common in CCMP patients (62.3% vs. 48.8% vs. 43.3%, respectively; p = 0.003). Concordantly, the central venous pressure/pulmonary capillary wedge pressure ratio, a useful predictor of RV dysfunction when >0.63, was significantly higher in CCMP patients compared with both NICMP and ICMP patients (0.68 vs. 0.54 vs. 0.51, respectively; p < 0.0001). Cardiac index and left ventricular ejection fraction did not differ among the groups, although heart rate was significantly higher in the CCMP group. Last, aspartate aminotransferase and alanine aminotransferase were twice as high in CCMP patients compared with ICMP patients and >1.5 times higher than in NICMP patients, but the differences were not statistically significant. Because actual RV risk scores could not be calculated for individual patients, comparisons of surrogate markers of RV dysfunction between the 3 groups are shown in Table 2.

Table 1 Continued

	CCMP (n = 75)	NICMP (n = 2,392)	p Value	ICMP (n = 1,345)	p Value
Laboratory					
Sodium, mmol/l	133	134	0.19	134	0.03
Creatinine, mg/dl	1.4	1.5	0.30	1.5	0.19
Blood urea nitrogen, mg/dl	28	30	0.26	32	0.06
Total bilirubin, mg/dl	1.5	1.6	0.56	1.4	0.27
Cholesterol, mg/dl	137	124	0.12	127.	0.24
INR, IU	1.28	1.41	0.0009	1.34	0.14
Hemoglobin, mg/dl	11.0	11.4	0.10	11.0	0.83
Platelet, K/μl	203	201	0.79	195	0.40
Protein C, %	72	83	0.53	81	0.63
Protein S, %	37	78	0.01	79	0.04
C-reactive protein, mg/l	16.9	20.4	0.81	24.1	0.71
B-type natriuretic peptide, pg/ml	1,762	1,333	0.06	1,191	0.01
Aspartate aminotransferase, μg/l	220	125	0.52	90	0.38
Alanine aminotransferase, μg/l	199	125	0.19	96	0.38
White blood cells, K/μl	8.4	9.1	0.06	9.2	0.04
Albumin, g/dl	3.3	3.3	0.87	3.2	0.43
Pre-albumin, mg/dl	18.3	17.9	0.79	17.5	0.61
Hemodynamics					
Systolic blood pressure, mm Hg	100	100	0.76	102	0.22
Diastolic blood pressure, mm Hg	63	63	0.70	62	0.22
Cardiac index, l/min/m^2	2.0	2.1	0.70	2.2	0.21
Heart rate, beats/min	100	91	0.0001	87	<0.0001
Right atrial pressure, mm Hg	16.5	13.5	0.01	12.5	0.0001
LVEDD, cm	5.89	6.95	<0.0001	6.73	<0.0001
Pulmonary wedge pressure, mm Hg	24.1	25.0	0.56	24.4	0.85
Pulmonary systolic pressure, mm Hg	43.9	49.4	0.0015	51.2	<0.0001
Pulmonary diastolic pressure, mm Hg	25.0	26.1	0.39	25.4	0.75
Pulmonary vascular resistance using cardiac output, Woods units	2.4	2.9	0.25	2.7	0.46
Mitral regurgitation (moderate/severe), %	68.0	61.0	0.28	56.0	0.08
Tricuspid regurgitation (moderate/severe), %	62.0	43.0	0.0037	49.0	0.04
Aortic regurgitation (moderate/severe), %	7.0	5.0	0.60	5.0	0.63
Left ventricular ejection fraction, %	25.9	14.0	0.38	25.7	0.48
Left ventricular ejection fraction (<20 severe), %	74.0	70.0	0.48	7.0	0.91
Right ventricular ejection fraction (severe), %	27.0	27.0	1.00	24.0	0.63
Operative, %					
Concomitant surgery	48.0	36.0	0.04	36.0	0.04
Left ventricular continuous flow device	84.0	74.0	0.06	78.0	0.25
Failure to wean from cardiopulmonary bypass	5.0	1.0	0.01	2.0	0.04

ACE = angiotensin-converting enzyme; CCMP = chemotherapy-induced cardiomyopathy; ICMP = ischemic cardiomyopathies; INR = international normalized ratio; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVEDD = left ventricular end-diastolic dimension; NICMP = nonischemic cardiomyopathies; NYHA = New York Heart Association.

Need for RVAD. Pre-operative RV failure resulted in concomitant RVAD implantation at the time of MCS surgery in 11 CCMP patients (14%), whereas post-LVAD RV failure required subsequent RVAD placement in another 3 CCMP patients (4%). Compared with all others, patients with CCMP had an increased need for RVAD (19% vs. 9.3%, $p < 0.0001$). When compared separately, the difference in RVAD need remained significant in CCMP, NICMP, and ICMP patients (19%, 11%, and 6%, respectively; $p = 0.006$) (Fig. 1). Interestingly, in this cohort, no total artificial hearts were implanted in CCMP patients as a bridge to transplantation.

Concomitant surgery and operative factors. Patients with CCMP had more concomitant surgery (48%) than patients with NICMP (36.5%; $p = 0.03$) and ICMP (36%; $p = 0.04$). Of these, tricuspid repair was the most common (n = 11; 15%), followed by RVAD implantation (n = 6; 8%), atrial septal defect closure (n = 4; 5%), and other (n = 18; 24%). Other concomitant surgeries included removal of temporary support devices (n = 7), aortic valve closure (n = 4), left atrial appendectomy (n = 2), femoral artery repair (n = 2), pericardial reconstruction (n = 2), and LV mass removal (n = 1).

CCMP patients were more likely to fail weaning from cardiopulmonary bypass compared with both NICMP and

Table 2 Surrogate Markers of Right Ventricular Function Among CCMP, NICMP, and ICMP

	CCMP (n = 75)	NICMP (n = 2,392)	p Value	ICMP (n = 1,345)	p Value
Inotropes, %	89.0	83.0	0.18	80.0	0.06
Ascites	13.0	9.0	0.29	9.0	0.24
Sodium, mmol/l	133	134	0.19	134	0.03
Creatinine, mg/dl	1.4	1.5	0.30	1.5	0.19
Blood urea nitrogen, mg/dl	28.0	30.6	0.26	32.06	0.06
Total bilirubin, mg/dl	1.5	1.6	0.56	1.4	0.27
Aspartate aminotransferase, μ/l	220	125	0.52	90	0.38
Alanine aminotransferase, μ/l	200	126	0.19	96	0.38
Systolic blood pressure, mm Hg	100	100	0.76	102	0.22
Diastolic blood pressure, mm Hg	63	63	0.70	62	0.22
Cardiac index, l/min/m^2	2.0	2.1	0.70	2.2	0.21
Heart rate, beats/min	100	92	0.0001	87	<0.0001
Right atrial pressure, mm Hg	16	13	0.01	12	0.0001
Pulmonary wedge pressure, mm Hg	24	25	0.56	24	0.85
CVP/PCWP ratio	0.68	0.54	<0.0001	0.51	<0.0001
Pulmonary systolic pressure, mm Hg	44	49	0.0015	51	<0.0001
Pulmonary diastolic pressure, mm Hg	25	26	0.39	25	0.75
Tricuspid regurgitation (moderate/severe), %	62.0	43.0	0.0037	49.0	0.04
Right ventricular ejection fraction (severe), %	27.0	27.0	1.00	24.0	0.63
Failure to wean from cardiopulmonary bypass, %	5.0	1.0	0.01	2.0	0.04

CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; other abbreviations as in Table 1.

ICMP patients (5.3% vs. 1.5% vs. 1.9%, respectively; p = 0.01 and 0.04, respectively).

The rate of continuous flow device use was the same in CCMP, NICMP, and ICMP patients (84%, 74.5%, and 78.4%, respectively).

Clinical outcomes and adverse events. Table 3 illustrates comparative outcomes in all groups. There was an increased risk of bleeding in CCMP patients compared with both ICMP and NICMP patients, but there was no difference in the time to neurological dysfunction, device malfunction, infection, or RV failure events (Fig. 2).

Survival. Survival of CCMP patients who received LVAD support was equivalent to that of other MCS patients. Survival in the groups is illustrated in Figure 3. CCMP patients who received biventricular assist device support did significantly worse than those who only received an LVAD.

There was no significant difference in the rates of death, transplantation, or recovery in any of the 3 groups (Table 3).

When cause of death was analyzed, there were 18 deaths in the CCMP group: multiorgan failure (n = 5; 28%), renal failure (n = 2; 11%), hemorrhage (n = 2; 11%), cerebrovascular event (n = 2; 11%), abdominal compartment syndrome (n = 1; 6%), pump failure (n = 2; 11%), cancer (n = 1; 6%), respiratory failure (n = 1; 6%), anoxic brain injury (n = 1; 6%), and sudden/unexplained (n = 1; 6%). Of these 18 deaths, 6 (33%) occurred among the 14 biventricular assist device patients.

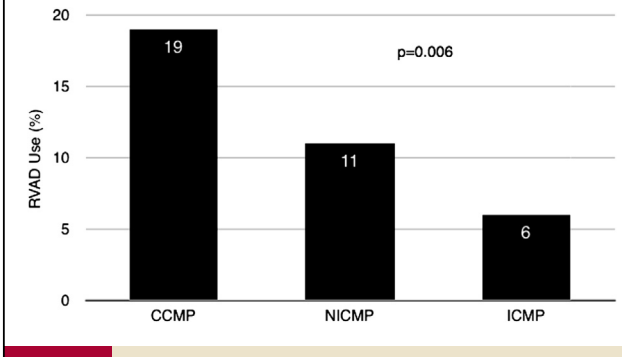

Figure 1 Need for RVAD Use According to Etiology of Cardiomyopathy

Incidence of need for RVAD use according to etiology of cardiomyopathy. CCMP = chemotherapy-induced cardiomyopathy; ICMP = ischemic cardiomyopathy; NICMP = nonischemic cardiomyopathy; RVAD = right ventricular assist device.

Discussion

This is the first report to date of a series of CCMP patients treated with MCS. We have found that survival of CCMP patients treated with MCS is similar to that of other MCS patients, but that CCMP is associated with a significantly higher risk of RV failure and need for RVAD support.

Table 3 Clinical Outcomes of All Groups

Outcome	CCMP (n = 75)	ICMP (n = 1,345)	NICMP (n = 2,466)	Total (N = 3,812)
Death	19 (25)	294 (22)	466 (19)	761 (20)
Transplantation	22 (29)	432 (32)	864 (36)	1,296 (34)
Recovery	1 (1)	3 (0.2)	41 (1)	44 (1)
Alive	33 (44)	616 (46)	1,095 (45)	1,711 (45)

Values are n (%). CCMP versus ICMP: p = 0.29; CCMP versus NICMP: p = 0.51; ICMP versus NICMP: p < 0.0001.
Abbreviations as in Table 1.

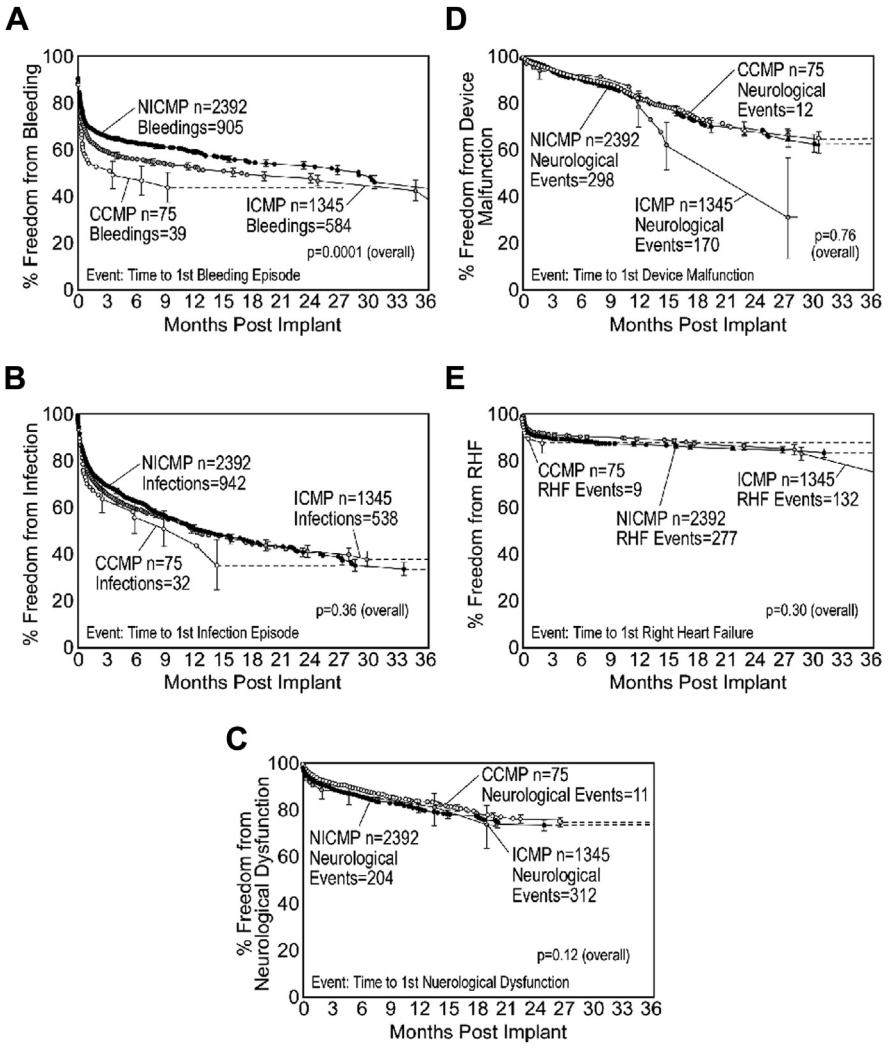

Figure 2 **Adverse Events in Patients With CCMP**

(A) Time to first bleeding. **(B)** Time to first infection. **(C)** Time to first neurological dysfunction. **(D)** Time to first device malfunction. **(E)** Time to first right heart failure event. RHF = right heart failure; other abbreviations as in Figure 1.

Therefore, while validating the usefulness of this technology for CCMP patients, we also demonstrate the prevalence of biventricular involvement in CCMP.

In this study, almost 1 in 5 patients with CCMP had RV failure that required RVAD support. Most likely, this high incidence reflects the learning curve in evaluating and avoiding RV failure, which has steadily improved over the time period studied. Other findings supportive of the higher frequency of RV involvement in CCMP were more frequent surrogate markers of RV dysfunction (12) and a higher incidence of preoperative severe tricuspid regurgitation (13,14) requiring tricuspid valve repair. Although the adverse event comparison appears to negate this assertion, it is important to remember that, in the adverse event analysis, RV failure is only considered post-operatively. This means that it also includes patients who had already received RVADs and were no longer at risk of RV failure.

The discovery that RV failure occurs in about one-fifth of CCMP patients is unique given that, in most cardiomyopathic processes, the pathogenesis of myocardial dysfunction has been shown to predominantly affect the left ventricle (15) and that ~90% of MCS patients can be treated with LVAD alone (16). Therefore, this knowledge should lead to increased awareness of the possibility of post-implantation RV failure when deciding to treat CCMP patients with MCS. Indeed, pre-emptive RVAD placement or the use of a total artificial heart may be preferred for these patients to avoid the increased morbidity and mortality associated with post-LVAD RV failure

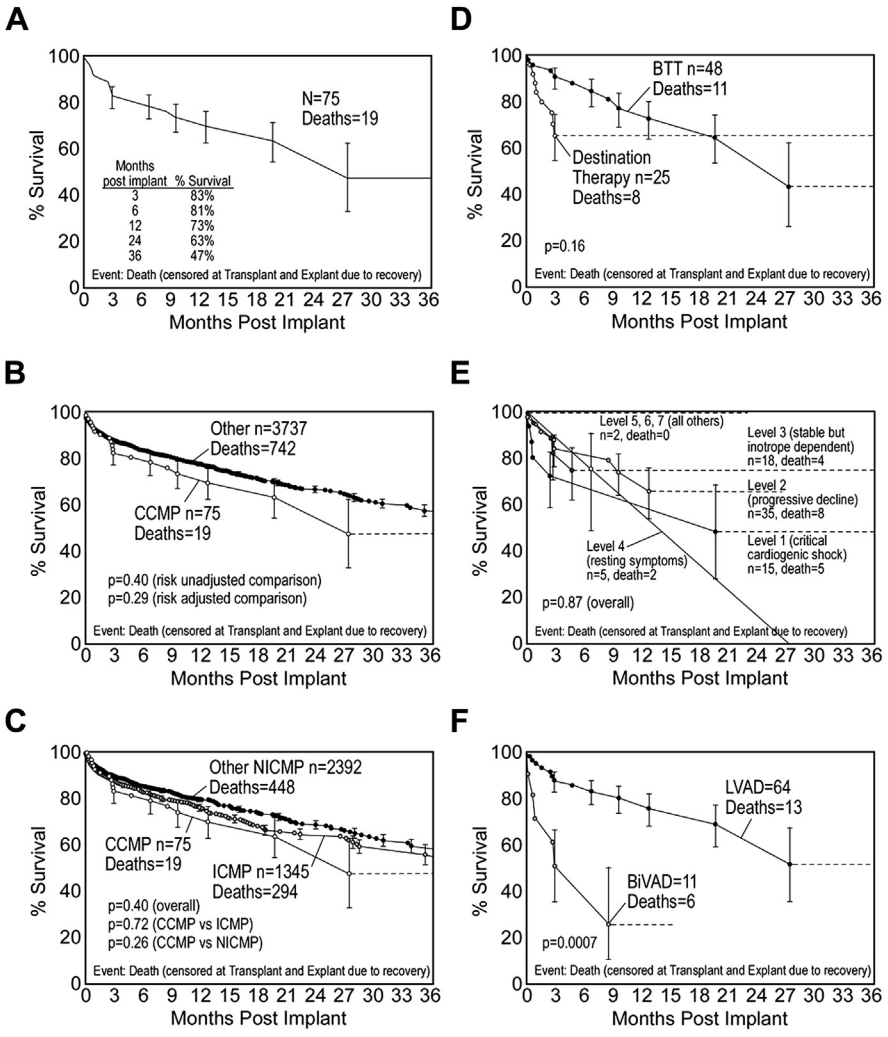

Figure 3 **Survival of Patients With CCMP**

(A) CCMP. **(B)** CCMP versus (ICMP and NICMP) adult primary implants. **(C)** CCMP versus ICMP versus NICMP adult primary implants. **(D)** CCMP patients by device strategy. **(E)** CCMP patient profile. **(F)** CCMP by device side. BTT = bridge to transplantation; BiVAD = biventricular assist device; LVAD = left ventricular assist device; other abbreviations as in Figure 1.

(17,18). This may be especially relevant in the setting of heart failure caused specifically by anthracyclines. Because anthracyclines such as doxorubicin were the cause of CCMP in our entire patient population, it is likely that increased RV failure is a feature more specific to anthracyclines than other agents, such as trastuzumab. Therefore, it may become important to determine with certainty the etiology of CCMP because, if the etiology is anthracyclines, RV function is likely to deteriorate proportionately to the left ventricular function, and univentricular support may not suffice. RV endomyocardial biopsy with typical characteristics of anthracycline cardiotoxicity is the only way to establish with certainty the etiology of heart failure in patients with CCMP (19–21), particularly because many potentially cardiotoxic agents are given simultaneously or in sequence to treat cancer. The pathological proof of anthracycline cardiotoxicity may therefore be instrumental in the decision-making process leading to the use of biventricular support. Conversely, biopsy determination of the absence of anthracycline injury, together with other measures of RV function, may help avoid unnecessary RVAD use, especially because, as previously shown (16) and demonstrated here, the need for biventricular assist device support portends a poorer prognosis. Unfortunately, optimal treatment of CCMP patients with severe RV failure continues to be limited by the absence of a commercially available U.S. Food and Drug Administration–approved durable intracorporeal RVAD. Indeed, in this cohort, patients who required RVAD support were treated with temporary paracorporeal systems.

This study confirms that the overwhelming majority of patients with CCMP who receive advanced heart failure

therapy are women, comprising about three-fourths of the patients in this cohort (5). Although the most likely explanation is the high prevalence of breast cancer survivors in this cohort, it is possible that women are more prone to the cardiotoxic effects of cancer therapy or that in women, the progression to end-stage heart failure is more common. If confirmed by future studies, increased monitoring and more robust cardioprotective measures, including consideration of prophylactic beta-blocker and angiotensin-converting enzyme inhibitor therapy, should be considered in women undergoing potentially cardiotoxic cancer treatment.

Although this study does not allow definitive conclusions that can be generalized about the characteristics of CCMP patients because this cohort is clearly not representative of the majority of patients with CCMP, it does provide important insights into physicians' patterns of practice relating to CCMP patients. A provocative observation is that despite being younger and having equivalent ejection fraction and heart failure severity, CCMP patients had significantly lower use of a prophylactic implantable cardioverter-defibrillator compared with both ICMP and NICMP patients. A possible explanation for this finding is that these patients may present too acutely for implantation of cardioverter-defibrillators. Also, CCMP patients selected for MCS had significantly lower use of alcohol, drugs, and tobacco as well as lower rates of diabetes. It is possible that, in general, CCMP patients display healthier behavior that stems from the fear of recurrent cancer, but it is also not inconceivable that because of the stigma associated with the etiology of their heart failure, they may be subjected to stricter requirements for MCS eligibility than their ICMP and NICMP counterparts. Last, the implantation strategy for CCMP patients was destination therapy much more frequently than for both NICMP and ICMP patients. This is likely a result of the usual 5-year cancer-free requirement for transplantation eligibility, as well as the type of previous cancers: some, like melanoma, may confer definitive ineligibility. Accordingly, our data show that if the original implantation strategy was a bridge to transplantation, CCMP patients were as likely as any other to be listed for transplantation.

Unexpectedly, there was no difference in the rates of post-implantation infections between the groups, although CCMP patients undergoing heart transplantation have been shown to be more prone to infectious complications (5). There was, however, increased bleeding in the CCMP group, but platelet levels, international normalized ratios, and protein C levels were similar. Protein S, however, was significantly lower in CCMP patients compared with both ICMP and NICMP patients. Higher, but not lower, protein S levels have been shown to be correlated with bleeding (22), and thus the lower levels of protein S in CCMP patients do not explain their increased bleeding risk. Although we found no differences in pre-implantation bleeding risk factors among the groups, it is possible that the higher rates of bleeding in CCMP patients are due to chemotherapy-induced bone marrow toxicity with decreased reserve. However, a more likely explanation is that patients who go into surgery more "congested," with higher central venous pressure, have been shown, at least anecdotally, to have more perioperative bleeding. Despite increased bleeding, only 2 patients died of hemorrhage, and overall comparative survival in CCMP patients was not adversely affected.

Study limitations. There are several limitations inherent to the database itself and to this type of study. One major imperfection of the database is illustrated here by the fact that the presence of cancer was only documented in 89% of patients with a history of anthracycline therapy. Because there are no other medical indications for anthracycline use, rather than suggesting that 11% of patients did not have cancer, this discrepancy only illustrates the incompleteness of cancer-related data entry for these patients. Accordingly, there are no reliable data on the type of cancer and, many times, the type of chemotherapy used, as well as the temporal relationship between chemotherapy and heart failure development. In fact, the attribution of heart failure etiology cannot be verified with certainty in the absence of biopsy data. Additionally, because patient identification information was not collected to protect patient privacy, the registry is unable to confirm death or heart transplantation with external sources such as the Social Security Death Index and the United Network of Organ Sharing database. Last, despite being the largest such series, the total number of patients with CCMP remains small, which may have hindered our ability to detect survival differences between CCMP patients and other groups.

Conclusions

CCMP patients treated with MCS have survival similar to that of other MCS patients despite having more frequent need of an RVAD and increased bleeding risk. Further studies are needed to better understand the nature of CCMP and to confirm our findings.

Reprint requests and correspondence: Dr. Guilherme H. Oliveira, Advanced Heart Failure and Transplantation Center, Division of Cardiovascular Medicine, Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, 11100 Euclid Avenue, LKS 3012, Cleveland, Ohio 44106. E-mail: guilherme.oliveira@UHhospitals.org.

REFERENCES

1. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 2012;60:2504–12.
2. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients

with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30:3792–9.
3. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606.
4. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077–84.
5. Oliveira GH, Hardaway BW, Kucheryavaya AY, Stehlik J, Edwards LB, Taylor DO. Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation. J Heart Lung Transplant 2012;31:805–10.
6. Costanzo MR, Dipchand A, Starling R, et al., International Society of Heart and Lung Transplantation. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914–56.
7. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson L, Miller M, Young JB. Long-term mechanical circulatory support (destination therapy): on track to compete with heart transplantation? J Thorac Cardiovasc Surg 2012;144:584–603, discussion 597–8.
8. Slaughter MS, Rogers JG, Milano CA, et al., HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.
9. Freilich M, Stub D, Esmore D, et al. Recovery from anthracycline cardiomyopathy after long-term support with a continuous flow left ventricular assist device. J Heart Lung Transplant 2009;28:101–3.
10. Simsir SA, Lin SS, Blue LJ, Gockerman JP, Russell SD, Milano CA. Left ventricular assist device as destination therapy in doxorubicin-induced cardiomyopathy. Ann Thorac Surg 2005;80:717–9.
11. Kirklin JK, Naftel DC, Stevenson LW, et al. INTERMACS database for durable devices for circulatory support: first annual report. J Heart Lung Transplant 2008;27:1065–72.
12. Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181–4.
13. Baumwol J, Macdonald PS, Keogh AM, et al. Right heart failure and "failure to thrive" after left ventricular assist device: clinical predictors and outcomes. J Heart Lung Transplant 2011;30:888–95.
14. Potapov EV, Stepanenko A, Dandel M, et al. Tricuspid incompetence and geometry of the right ventricle as predictors of right ventricular function after implantation of a left ventricular assist device. J Heart Lung Transplant 2008;27:1275–81.
15. Yilmaz A, Kindermann I, Kindermann M, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation 2010;122:900–9.
16. Cleveland JC Jr., Naftel DC, Reece TB, et al. Survival after biventricular assist device implantation: an analysis of the Interagency Registry for Mechanically Assisted Circulatory Support database. J Heart Lung Transplant 2011;30:862–9.
17. Dang NC, Topkara VK, Mercando M, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant 2006;25:1–6.
18. Fitzpatrick JR 3rd, Frederick JR, Hiesinger W, et al. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. J Thorac Cardiovasc Surg 2009;137:971–7.
19. Friedman MA, Bozdech MJ, Billingham ME, Rider AK. Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. JAMA 1978;240:1603–6.
20. Billingham ME. Pharmacotoxic myocardial disease: an endomyocardial study. Heart Vessels Suppl 1985;1:278–82.
21. Freter CE, Lee TC, Billingham ME, Chak L, Bristow MR. Doxorubicin cardiac toxicity manifesting seven years after treatment. Case report and review. Am J Med 1986;80:483–5.
22. Rojnuckarin P, Uaprasert N, Akkawat B, Settapiboon R, Nanakorn T, Intragumtornchai T. Protein C, protein S and von Willebrand factor levels correlate with bleeding symptoms: a population-based study. Haemophilia 2012;18:457–62.

Key Words: assist devices ▪ chemotherapy-induced cardiomyopathy ▪ heart failure.